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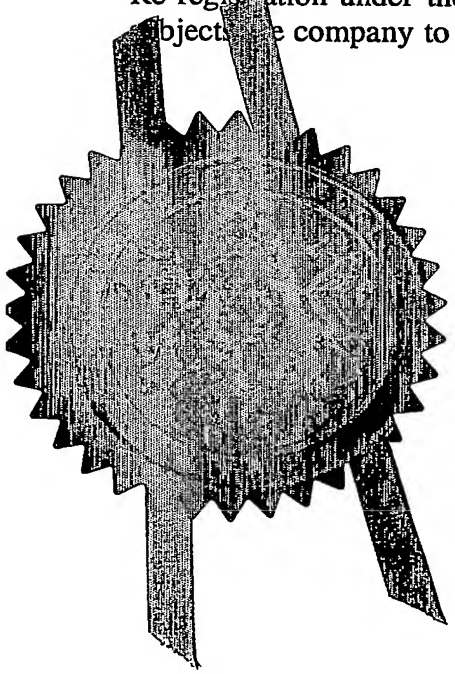

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Patents Form 1/77

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Cardiff Road
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1. Your reference — N.86243 JCI

2. Patent application number *(The Patent Office will fill in this pa)* — 0218473.7 — 08 AUG 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PHARMA PACIFIC PTY. LTD.
103-105 Pipe Road
Laverton North
Victoria 3026
AUSTRALIA

Patents ADP number *(if you know it)* 7589484003

If the applicant is a corporate body, give the country/state of its incorporation — AUSTRALIA

4. Title of the invention — INTERFERON-ALPHA INDUCED GENE

5. Name of your agent *(if you have one)* — J.A. KEMP & CO.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

14 South Square
Gray's Inn
London
WC1R 5JJ

Patents ADP number *(if you know it)* 26001

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

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Description	48
Claim *(s)*	4
Abstract	1
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Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this applica

Signature J.A. Kemp & Co. Date 8 August 200

J.A. KEMP & CO.

12. Name and daytime telephone number of person to contact in the United Kingdom

IRVINE, Jonquil Claire
020 7405 3292

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INTERFERON-ALPHA INDUCED GENE

Field of the Invention

The present invention relates to identification of a human gene upregulated by interferon-α (IFN-α) administration, the coding sequence of which is believed to be previously unknown. Detection of expression products of this gene may find use in predicting responsiveness to IFN-α and other interferons which act at the Type 1 interferon receptor. Therapeutic use of the isolated novel protein encoded by the same gene is also envisaged.

Background of the Invention

IFN-α is widely used for the treatment of a number of disorders. Disorders which may be treated using IFN-α include neoplastic diseases such as leukemia, lymphomas, and solid tumours, AIDS-related Kaposi's sarcoma and viral infections such as chronic hepatitis. IFN-α has also been proposed for administration via the oromucosal route for the treatment of autoimmune, mycobacterial, neurodegenerative, parasitic and viral disease. In particular, IFN-α has been proposed, for example, for the treatment of multiple sclerosis, leprosy, tuberculosis, encephalitis, malaria, cervical cancer, genital herpes, hepatitis B and C, HIV, HPV and HSV-1 and 2. It has also been suggested for the treatment of arthritis, lupus and diabetes. Neoplastic diseases such as multiple myeloma, hairy cell leukemia, chronic myelogenous leukemia, low grade lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, cervical cancer, sarcomas including Kaposi's sarcoma, kidney tumours, carcinomas including renal cell carcinoma, hepatic cellular carcinoma, nasopharyngeal carcinoma, haematological malignancies, colorectal cancer, glioblastoma, laryngeal papillomas, lung cancer, colon cancer, malignant melanoma and brain tumours are also suggested as being treatable by administration of IFN-α via the oromucosal route, i.e. the oral route or the nasal route.

IFN-α is a member of the Type 1 interferon family, which exert their characteristic biological activities through interaction with the Type 1 interferon receptor. Other Type 1 interferons include IFN-β, IFN-ω and IFN-τ.

Unfortunately, not all potential patients for treatment with a Type 1 interferon such as interferon-α, particularly, for example, patients suffering from chronic viral

hepatitis, neoplastic disease and relapsing remitting multiple sclerosis, respond favourably to Type 1 interferon therapy and only a fraction of those who do respond exhibit long-term benefit. The inability of the physician to confidently predict the therapeutic outcome of Type 1 interferon treatment raises serious concerns as to the cost-benefit ratio of such treatment, not only in terms of wastage of an expensive biopharmaceutical and lost time in therapy, but also in terms of the serious side effects to which the patient is exposed. Furthermore, abnormal production of IFN-α has been shown to be associated with a number of autoimmune diseases. For these reasons, there is much interest in identifying Type 1 interferon responsive genes since Type1 interferons exert their therapeutic action by modulating the expression of a number of genes. Indeed, it is the specific pattern of gene expression induced by Type 1 interferon treatment that determines whether a patient will respond favourably or not to the treatment.

Summary of the Invention

A human gene cDNA has now been identified as corresponding to a mouse gene upregulated by administration of IFN-α by an oromucosal route or intravenously and is believed to represent a novel DNA. The corresponding human gene is thus now also designated an IFN-α upregulated gene.

The HuIFRG 217.1 gene encodes a protein of 1,933 amino acids and is referred to below as HuIFRG 217.1 protein. This protein shows homology to a 1298 amino acid protein (KIAA 268), a 419 amino acid protein (AK022542) and a 556 amino acid protein (AK00177C) all of unknown function. The sequences of these proteins are publicly available, for example from the GenBank™ database. The HuIFRG 217.1 protein is also related to an earlier published polypeptide known as HuIFRG 70, the amino acid sequence of which is given in SEQ ID NO: 4. HuIFRG 217.7 and HuIFRG 70 are different transcripts of the same gene. It is believed that the HuIFRG 70 transcript is a shorter variant of the mature HuIFRG 217.1 mature protein. The existence of HuIFRG 217.1 was previously unrecognised. HuIFRG 217.1 protein, and functional variants thereof, are now envisaged as therapeutic agents, in particular for use as an anti-viral, anti-tumour or immunomodulatory agent. For example, they may be used in the treatment of autoimmune, mycobacterial, neurodegenerative, parasitic or viral disease,

arthritis, diabetes, lupus, multiple sclerosis, leprosy, tuberculosis, encephalitis, malaria, cervical cancer, genital herpes, hepatitis B or C, HIV, HPV, HSV-1 or 2, or neoplastic disease such as multiple myeloma, hairy cell leukemia, chronic myelogenous leukemia, low grade lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, cervical cancer, sarcomas including Kaposi's sarcoma, kidney tumours, carcinomas including renal cell carcinoma, hepatic cellular carcinoma, nasopharyngeal carcinoma, haematological malignancies, colorectal cancer, glioblastoma, laryngeal papillomas, lung cancer, colon cancer, malignant melanoma or brain tumours. In other words, such a protein may find use in treating any Type 1 interferon treatable disease.

Determination of the level of HuIFRG 217.1 protein or a naturally-occurring variant thereof, or the corresponding mRNA, in cell samples of Type 1 interferon-treated patients, e.g. patients treated with IFN-α, e.g. such as by the oromucosal route or intravenously, may also be used to predict responsiveness to such treatment. It is believed that alternatively, and more preferably, such responsiveness may be judged, for example, by treating a sample of human peripheral blood mononuclear cells *in vitro* with a Type 1 interferon and looking for upregulation or downregulation of an expression product, preferably mRNA, corresponding to the HuIFRG 217.1 gene.

According to a first aspect of the invention, there is thus provided an isolated polypeptide comprising;

(i) the amino acid sequence of SEQ ID NO: 2;

(ii) an allelic or species variant of a sequence of (i);

(iii) a variant of a sequence of (i) having at least 60% identity over the full length of SEQ ID NO: 2 and having substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity; or

(iv) a fragment of (i) or (ii) which does not have the amino acid sequence of any of SEQ ID NO: 4, an allelic or species variant of the sequence of SEQ ID NO: 4 or a fragment thereof; and which retains substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity.

The invention also provides such a protein for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or

immunomodulatory agent. As indicated above, such use may extend to any Type 1 interferon treatable disease.

According to another aspect of the invention, there is provided an isolated polynucleotide encoding a polypeptide of the invention as defined above or a complement thereof. Such a polynucleotide will typically include a sequence comprising:

(a) the nucleic acid of SEQ. ID. No. 1 or the coding sequence thereof and/or a sequence complementary thereto;

(b) a sequence which hybridises, e.g. under stringent conditions, to a sequence complementary to a sequence as defined in (a);

(c) a sequence which is degenerate as a result of the genetic code to a sequence as defined in (a) or (b);

(d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c).

A polynucleotide of the invention will typically be a polynucleotide as described above but will not encode a polypeptide selected from:

(i) the amino acid sequence of SEQ ID NO: 4;

(ii) a variant thereof having substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity; or

(iii) a fragment of (i) or (ii) which retains substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity.

A polynucleotide of the invention will typically not consist of:

(a) the nucleic acid sequence of SEQ ID NO: 3 or the coding sequence thereof and/or a sequence complementary thereto;

(b) a sequence which hybridises to a sequence as defined in (a);

(c) a sequence that is degenerate as a result of the genetic code to a sequence as defined in (a) or (b); or

(d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c).

The invention also provides;

- an expression vector which comprises a polynucleotide of the invention and which is capable of expressing a polypeptide of the invention;
- a host cell containing an expression vector of the invention;
- an antibody specific for a polypeptide of the invention;
- a method of treating a subject having a Type 1 interferon treatable disease, which method comprises administering to the said patient an effective amount of HuIFRG 217.1 protein or a functional variant thereof,
- use of such a polypeptide in the manufacture of a medicament for use in therapy as an anti-viral or anti-tumour or immunomodulatory agent, more particularly for use in treatment of a Type 1 interferon treatable disease;
- a pharmaceutical composition comprising a polypeptide of the invention and a pharmaceutically acceptable carrier or diluent;
- a method of producing a polypeptide of the invention, which method comprises maintaining host cells of the invention under conditions suitable for obtaining expression of the polypeptide and isolating the said polypeptide;
- a polynucleotide of the invention, e.g. in the form of an expression vector, which directs expression *in vivo* of a polypeptide as defined above for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent;
- a pharmaceutical composition comprising such a polynucleotide and a pharmaceutically acceptable carrier or diluent;
- a method of treating a subject having a Type 1 interferon treatable disease, which method comprises administering to said patient an effective amount of such a polynucleotide;
- use of such a polynucleotide in the manufacture of a medicament, e.g. a vector preparation, for use in therapy as an anti-viral, anti-tumour or immunomodulatory agent, more particularly for use in treating a Type 1 interferon treatable disease; and
- a method of identifying a compound having immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity comprising providing a cell capable of expressing HuIFRG 217.1 protein or a naturally occurring variant thereof,

incubating said cell with a compound under test and monitoring for upregulation of HuIFRG 217.1 gene expression.

In a still further aspect, the invention provides a method of predicting responsiveness of a patient to treatment with a Type 1 interferon, e.g. IFN-α treatment (such as IFN-α treatment by the oromucosal route or a parenteral route, for example, intravenously, subcutaneously, or intramuscularly), which comprises determining the level of HuIFRG 217.1 protein or a naturally-occurring variant thereof, e.g. an allelic variant, or the corresponding mRNA, in a cell sample from said patient, e.g. a blood sample, wherein said sample is obtained from said patient following administration of a Type 1 interferon, e.g. IFN-α by an oromucosal route or intravenously, or is treated prior to said determining with a Type 1 interferon such as IFN-α *in vitro*. The invention also extends to kits for carrying out such testing.

Brief description of the Sequences

SEQ. ID. No.1 is the amino acid sequence of human protein HuIFRG 217.1 and its encoding cDNA.

SEQ. ID. No.2 is the amino acid sequence alone of HuIFRG 217.1 protein.

SEQ. ID. No. 3 is the amino acid sequence of human protein HuIFRG 70 and its encoding cDNA.

SEQ. ID. No. 4 is the amino acid sequence alone of HuIFRG 70 protein.

Detailed Description of the Invention

As indicated above, human protein HuIFRG 217.1 and functional variants thereof are now envisaged as therapeutically useful agents, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent.

A variant of HuIFRG 217.1 protein for this purpose may be a naturally occurring variant, either an allelic variant or species variant, which has substantially the same functional activity as HuIFRG 217.1 protein and is also upregulated in response to administration of IFN-α. Alternatively, a variant of HuIFRG 217.1 protein for therapeutic use may comprise a sequence which varies from SEQ. ID. No. 2 but which is a non-natural mutant.

The term " functional variant" refers to a polypeptide which has the same essential character or basic function of HuIFRG 217.1 protein. The essential character of HuIFRG 217.1 protein may be deemed to be as an immunomodulatory peptide. A functional variant polypeptide may show additionally or alternatively anti-viral activity and/or anti-tumour activity.

Desired anti-viral activity may, for example, be tested as follows. A sequence encoding a variant to be tested is cloned into a retroviral vector such as a retroviral vector derived from the Moloney murine leukemia virus (MoMuLV) containing the viral packaging signal ψ, and a drug-resistance marker. A pantropic packaging cell line containing the viral *gag*, and *pol*, genes is then co-transfected with the recombinant retroviral vector and a plasmid, pVSV-G, containing the vesicular stomatitis virus envelope glycoprotein in order to produce high-titre infectious replication incompetent virus (Burns *et al.*, Proc. Natl. Acad. Sci. USA **84**, 5232-5236). The infectious recombinant virus is then used to transfect interferon sensitive fibroblasts or lymphoblastoid cells and cell lines that stably express the variant protein are then selected and tested for resistance to virus infection in a standard interferon bio-assay (Tovey *et al.*, Nature, **271**, 622-625, 1978). Growth inhibition using a standard proliferation assay (Mosmann, T., J. Immunol. Methods, **65**, 55-63, 1983) and expression of MHC class I and class II antigens using standard techniques may also be determined.

A desired functional variant of HuIFRG 217.1 may consist essentially of the sequence of SEQ. ID. No. 2. A functional variant of SEQ. ID. No.2 may be a polypeptide which has a least 60% to 70% identity, preferably at least 80% or at least 90% and particularly preferably at least 95%, at least 97% or at least 99% identity with the amino acid sequence of SEQ. ID. No. 2 over a region of at least 20, preferably at least 30, for instance at least 100 contiguous amino acids or over the full length of SEQ. ID. No. 2. In one aspect a desired functional variant shows such a degree of homology over a region of at least 20, preferably at least 30, for instance at least 100 contiguous amino acids of SEQ ID NO. 2, but does not show such homology to the amino acid sequence of SEQ ID No. 4. Preferably a desired functional variant shows such a degree of homology over the entire length of SEQ ID NO. 2. For example, a variant may show at least 60%, at least 70%, at least 80% or at least 90% and preferably at least 95%, at

least 97% or at least 99% identity over the full length of the amino acid sequence of SEQ. ID. No. 2. Methods of measuring protein identity are well known in the art.

Amino acid substitutions may be made, for example from 1, 2 or 3 to 10, 20 or 30 substitutions. Conservative substitutions may be made, for example according to the following Table. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other:

ALIPHATIC	Non-polar	G A P
		I L V
	Polar-uncharged	C S T M
		N Q
	Polar-charged	D E
		K R
AROMATIC		H F W Y

Variant polypeptide sequences for therapeutic use in accordance with the invention may be shorter polypeptide sequences, for example, a peptide of at least 20 amino acids or up to 50, 60, 70, 80, 100, 150 or 200 amino acids in length is considered to fall within the scope of the invention provided it retains appropriate biological activity of HulFRG 217.1 protein. In particular, but not exclusively, this aspect of the invention encompasses the situation when the variant is a fragment of a complete naturally-occurring protein sequence. A preferred fragment of HulFRG 217.1 protein is derived from a region of the HulFRG 217.1 amino acid sequence which is not also found in the HulFRG 70 amino acid sequence given in SEQ ID No. 4. Such a fragment may consist entirely of an amino acid sequence which is not present in SEQ ID No. 4. That is, such a fragment may not comprise the amino acid sequence of SEQ ID NO. 4 or a fragment thereof. Such a fragment of the invention may be a fragment of the amino acid sequence of SEQ ID NO. 2 that includes part of the sequence of SEQ ID NO. 4 and additionally extends beyond the ends of that polypeptide to include further amino acids which are present in SEQ ID NO. 2 but not SEQ ID NO. 4.

Also encompassed by the invention are modified forms of HuIFRG 217.1 protein and fragments thereof which can be used to raise anti-HuIFRG 217.1 protein antibodies. Such variants will comprise an epitope of the HuIFRG 217.1 protein. Preferably, such variants will comprise an epitope of the HuIFRG 217.1 protein which is not present in the HuIFRG 70 protein.

Polypeptides of the invention may be chemically modified, e.g. post-translationally modified. For example, they may be glycosylated and/or comprise modified amino acid residues. They may also be modified by the addition of a sequence at the N-terminus and/or C-terminus, for example by provision of histidine residues or a T7 tag to assist their purification or by the addition of a signal sequence to promote insertion into the cell membrane. Such modified polypeptides fall within the scope of the term "polypeptide" of the invention.

A polypeptide of the invention may be labelled with a revealing label. The revealing label may be any suitable label which allows the polypeptide to be detected. Suitable labels include radioisotopes such as ^{125}I, ^{35}S or enzymes, antibodies, polynucleotides and linkers such as biotin. Labelled polypeptides of the invention may be used in assays. In such assays it may be preferred to provide the polypeptide attached to a solid support. The present invention also relates to such labelled and/or immobilised polypeptides packaged in the form of a kit in a container. The kit may optionally contain other suitable reagent(s), control(s) or instructions and the like.

The polypeptides of the invention may be made synthetically or by recombinant means. Such polypeptides of the invention may be modified to include non-naturally occurring amino acids, e.g. D amino acids. Variant polypeptides of the invention may have modifications to increase stability *in vitro* and/or *in vivo*. When the polypeptides are produced by synthetic means, such modifications may be introduced during production. The polypeptides may also be modified following either synthetic or recombinant production.

A number of side chain modifications are known in the protein modification art and may be present in polypeptides of the invention. Such modifications include, for example, modifications of amino acids by reductive alkylation by reaction with an aldehyde followed by reduction with $NaBH_4$, amidination with methylacetimidate or acylation with acetic anhydride.

Polypeptides of the invention will be in substantially isolated form. It will be understood that the polypeptides may be mixed with carriers or diluents which will not interfere with the intended purpose of the polypeptide and still be regarded as substantially isolated. A polypeptide of the invention may also be in substantially purified form, in which case it will generally comprise the polypeptide in a preparation in which more than 90%, for example more than 95%, 98% or 99%, by weight of polypeptide in the preparation is a polypeptide of the invention.

Polynucleotides

The invention also includes isolated nucleotide sequences that encode HuIFRG 217.1 protein or a variant thereof as well as isolated nucleotide sequences which are complementary thereto. The nucleotide sequence may be DNA or RNA, single or double stranded, including genomic DNA, synthetic DNA or cDNA. Preferably the nucleotide sequence is a DNA sequence and most preferably, a cDNA sequence.

As indicated above, such a polynucleotide will typically include a sequence comprising:

(a) the nucleic acid of SEQ. ID. No. 1 or the coding sequence thereof and/or a sequence complementary thereto;

(b) a sequence which hybridises, e.g. under stringent conditions, to a sequence complementary to a sequence as defined in (a);

(c) a sequence which is degenerate as a result of the genetic code to a sequence as defined in (a) or (b);

(d) a sequence having at least 60% identity to a sequence as defined in (a),(b) or (c).

Polynucleotides comprising an appropriate coding sequence can be isolated from human cells or synthesised according to methods well known in the art, as described by way of example in Sambrook *et al.* (1989) Molecular Cloning: A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory Press.

Polynucleotides of the invention may include within them synthetic or modified nucleotides. A number of different types of modification to polynucleotides are known in the art. These include methylphosphonate and phosphothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. Such modifications

may be carried out in order to enhance the *in vivo* activity or lifespan of polynucleotides of the invention.

Typically a polynucleotide of the invention will include a sequence of nucleotides, which may preferably be a contiguous sequence of nucleotides, which is capable of hybridising under selective conditions to the coding sequence or the complement of the coding sequence of SEQ. ID. No. 1. A polynucleotide of the invention may be a species or allelic variant of the polynucleotide sequence of coding sequence of SEQ ID NO: 1. Such hybridisation will occur at a level significantly above background. Background hybridisation may occur, for example, because of other cDNAs present in a cDNA library. The signal level generated by the interaction between a polynucleotide of the invention and the coding sequence or complement of the coding sequence of SEQ. ID. No. 1 will typically be at least 10 fold, preferably at least 100 fold, as intense as interactions between other polynucleotides and the coding sequence of SEQ. ID. No. 1. The intensity of interaction may be measured, for example, by radiolabelling the probe, e.g. with ^{32}P. Selective hybridisation may typically be achieved using conditions of low stringency (0.3M sodium chloride and 0.03M sodium citrate at about 40°C), medium stringency (for example, 0.3M sodium chloride and 0.03M sodium citrate at about 50°C) or high stringency (for example, 0.03M sodium chloride and 0.03M sodium citrate at about 60°C).

Preferably the polynucleotide of the invention is not the polynucleotide shown in SEQ ID NO. 3, the coding sequence thereof, the complement thereof or a fragment thereof. Preferably, the polynucleotide is capable of hybridising under such selective conditions to the coding sequence or the complement thereof of SEQ ID No.1, but is not capable of hybridising under such conditions to the coding sequence or the complement of the coding sequence of SEQ ID No. 3.

The coding sequence of SEQ ID No: 1 may be modified by nucleotide substitutions, for example from 1, 2 or 3 to 10, 25, 50 or 100 substitutions. Degenerate substitutions may be made and/or substitutions may be made which would result in a conservative amino acid substitution when the modified sequence is translated, for example as shown in the table above. The coding sequence of SEQ. ID. NO: 1 may alternatively or additionally be modified by one or more insertions and/or deletions and/or by an extension at either or both ends.

A polynucleotide of the invention capable of selectively hybridising to a DNA sequence selected from SEQ. ID No.1, the coding sequence thereof and DNA sequences complementary thereto will be generally at least 60%, preferably at least 70, 80 or 90% and more preferably at least 95% or 97%, homologous to the target sequence. This homology may typically be over a region of at least 20, preferably at least 30, for instance at least 40, 60 or 100 or more contiguous nucleotides. This homology may be over the entire length of the target sequence. Preferably a polynucleotide of the invention shows such homology to the sequence of SEQ ID NO. 1 or a region thereof but does not show such homology to the sequence of SEQ ID No.3.

Any combination of the above mentioned degrees of homology and minimum sized may be used to define polynucleotides of the invention, with the more stringent combinations (i.e. higher homology over longer lengths) being preferred. Thus for example a polynucleotide which is at least 80% homologous over 25, preferably over 30 nucleotides forms may be found suitable, as may be a polynucleotide which is at least 90% homologous over 40 nucleotides.

Homologues of polynucleotide or protein sequences as referred to herein may be determined in accordance with well-known means of homology calculation, e.g. protein homology may be calculated on the basis of amino acid identity (sometimes referred to as "hard homology"). For example the UWGCG Package provides the BESTFIT program which can be used to calculate homology, for example used on its default settings, (Devereux *et al.* (1984) Nucleic Acids Research **12**, 387-395). The PILEUP and BLAST algorithms can be used to calculate homology or line up sequences or to identify equivalent or corresponding sequences, typically used on their default settings, for example as described in Altschul S. F. (1993) J. Mol. Evol. **36**,290-300; Altschul, S. F. *et al.* (1990) J. Mol. Biol. **215**,403-10.

Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence that either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighbourhood word score threshold (Altschul *et al.*, supra). These initial neighbourhood word hits act as seeds for initiating searches to find

HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extensions for the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1992) Proc. Natl. Acad. Sci. USA 89,10915-10919) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

The BLAST algorithm performs a statistical analysis of the similarity between two sequences; see e.g., Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90: 5873-5787. One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a sequence is considered similar to another sequence if the smallest sum probability in comparison of the first sequence to the second sequence is less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

Polynucleotides according to the invention have utility in production of the proteins according to the invention, which may take place *in vitro, in vivo* or *ex vivo.* In such a polynucleotide, the coding sequence for the desired protein of the invention will be operably linked to a promoter sequence which is capable of directing expression of the desired protein in the chosen host cell. Such a polynucleotide will generally be in the form of an expression vector. Polynucleotides of the invention, e.g. in the form of an expression vector, which direct expression *in vivo* of a polypeptide of the invention having immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity may also be used as a therapeutic agent.

Expression vectors for such purposes may be constructed in accordance with conventional practices in the art of recombinant DNA technology. They may, for example, involve the use of plasmid DNA. They may be provided with an origin of replication. Such a vector may contain one or more selectable markers genes, for

example an ampicillin resistance gene in the case of a bacterial plasmid. Other features of vectors of the invention may include appropriate initiators, enhancers and other elements, such as for example polyadenylation signals which may be desirable, and which are positioned in the correct orientation, in order to allow for protein expression. Other suitable non-plasmid vectors would be apparent to persons skilled in the art. By way of further example in this regard reference is made again to Sambrook *et al.*, 1989 (supra). Such vectors additionally include, for example, viral vectors. Examples of suitable viral vectors include herpes simplex viral vectors, replication-defective retroviruses, including lentiviruses, adenoviruses, adeno-associated virus, HPV viruses (such as HPV-16 and HPV-18) and attenuated influenza virus vectors.

Promoters and other expression regulation signals may be selected to be compatible with the host cell for which expression is designed. For example, yeast promoters include *S. cerevisiae* GAL4 and ADH promoters, *S. pombe nmt*1 and *adh* promoter. Mammalian promoters include the metallothionein promoter which can be induced in response to heavy metals such as cadmium and β-actin promoters. Viral promoters such as the SV40 large T antigen promoter or adenovirus promoters may also be used. Other examples of viral promoters which may be employed include the Moloney murine leukemia virus long terminal repeat (MMLV LTR), the rous sarcoma virus (RSV) LTR promoter, the human cytomegalovirus (CMV) IE promoter, and HPV promoters, particularly the HPV upstream regulatory region (URR). Other suitable promoters will be well-known to those skilled in the recombinant DNA art.

An expression vector of the invention may further include sequences flanking the coding sequence for the desired polypeptide of the invention providing sequences homologous to eukaryotic genomic sequences, preferably mammalian genomic sequences, or viral genomic sequences. This will allow the introduction of such polynucleotides of the invention into the genome of eukaryotic cells or viruses by homologous recombination. In particular, a plasmid vector comprising the expression cassette flanked by viral sequences can be used to prepare a viral vector suitable for delivering the polynucleotides of the invention to a mammalian cell.

The invention also includes cells *in vitro*, for example prokaryotic or eukaryotic cells, which have been modified to express the HuIFRG 217.1 protein or a variant thereof. Such cells include stable, e.g. eukaryotic, cell lines wherein a polynucleotide

encoding HuIFRG 217.1 protein or a variant thereof is incorporated into the host genome. Host cells of the invention may be mammalian cells or insect cells, lower eukaryotic cells, such as yeast or prokaryotic cells such as bacterial cells. Particular examples of cells which may be modified by insertion of vectors encoding for a polypeptide according to the invention include mammalian HEK293T, CHO, HeLa and COS cells. Preferably a cell line may be chosen which is not only stable, but also allows for mature glycosylation of a polypeptide. Expression may, for example, be achieved in transformed oocytes.

A polypeptide of the invention may be expressed in cells of a transgenic non-human animal, preferably a mouse. A transgenic non-human animal capable of expressing a polypeptide of the invention is included within the scope of the invention.

Polynucleotides according to the invention may also be inserted into vectors as described above in an antisense orientation in order to provide for the production of antisense sequences. Antisense RNA or other antisense polynucleotides may also be produced by synthetic means.

A polynucleotide, e.g. in the form of an expression vector, capable of expressing *in vivo* an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ. ID. No. 2, or a naturally-occurring variant thereof, for use in therapeutic treatment of a human or non-human animal is also envisaged as constituting an additional aspect of the invention. Such a polynucleotide will find use in treatment of diseases associated with upregulation of HuIFRG 217.1 protein.

Polynucleotides of the invention extend to sets of primers for nucleic acid amplification which target sequences within the cDNA for a polypeptide of the invention, e.g. pairs of primers for PCR amplification. The invention also provides probes suitable for targeting a sequence within a cDNA or RNA for a polypeptide of the invention which may be labelled with a revealing label, e.g. a radioactive label or a non-radioactive label such as an enzyme or biotin. Such probes may be attached to a solid support. Such a solid support may be a micro-array (also commonly referred to as nucleic acid, probe or DNA chip) carrying probes for further nucleic acids, e.g. mRNAs or amplification products thereof corresponding to other Type 1 interferon upregulated genes, e.g. such genes identified as upregulated in response to oromucosal or intravenous administration of IFN-α. Methods for constructing such micro-arrays are well-known

(see, for example, EP-B 0476014 and 0619321 of Affymax Technologies N.V. and Nature Genetics Supplement January 1999 entitled "The Chipping Forecast").

The nucleic acid sequence of such a primer or probe will preferably be at least 10, preferably at least 15 or at least 20, for example at least 25, at least 30 or at least 40 nucleotides in length. It may, however, be up to 40, 50, 60, 70, 100 or 150 nucleotides in length or even longer. Preferably the primer or probe is chosen to target sequences within the cDNA for the HuIFRG 217.1 protein which are not present in the cDNA for the HuIFRG 70 protein.

Another aspect of the invention is the use of probes or primers of the invention to identify mutations in HuIFRG 217.1 genes, for example single nucleotide polymorphisms (SNPs).

As indicated above, in a still further aspect the present invention provides a method of identifying a compound having immunomodulatory activity and/or antiviral activity and/or anti-tumour activity comprising providing a cell capable of expressing HuIFRG 217.1 protein or a naturally-occurring variant thereof, incubating said cell with a compound under test and monitoring for upregulation of HuIFRG 217.1 gene expression. Such monitoring may be by probing for mRNA encoding HuIFRG 217.1 protein or a naturally-occurring variant thereof. Alternatively antibodies or antibody fragments capable of specifically binding one or more of HuIFRG 217.1 and naturally-occurring variants thereof may be employed.

Antibodies

According to another aspect, the present invention also relates to antibodies (for example polyclonal or preferably monoclonal antibodies, chimeric antibodies, humanised antibodies and fragments thereof which retain antigen-binding capability) which have been obtained by conventional techniques and are specific for a polypeptide of the invention. Such antibodies could, for example, be useful in purification, isolation or screening methods involving immunoprecipitation and may be used as tools to further elucidate the function of HuIFRG 217.1 protein or a variant thereof. They may be therapeutic agents in their own right. Such antibodies may be raised against specific epitopes of proteins according to the invention. Antibodies of the invention are antibodies which bind specifically to the HuIFRG 271.1 protein. In one embodiment,

such an antibody specifically binds an epitope within the HuIFRG217.1 protein, but does not specifically bind the HuIFRG 70 protein. An antibody specifically binds to a protein when it binds with high affinity to the protein for which it is specific but does not bind or binds with only low affinity to other proteins. A variety of protocols for competitive binding or immunoradiometric assays to determine the specific binding capability of an antibody are well-known.

Pharmaceutical compositions

A polypeptide of the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. The pharmaceutical carrier or diluent may be, for example, an isotonic solution. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methyl cellulose, carboxymethylcellulose or polyvinyl pyrrolidone; desegregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methyl cellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for intravenous administration or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

A suitable dose of HuIFRG 217.1 protein or a functional analogue thereof for use in accordance with the invention may be determined according to various parameters, especially according to the substance used; the age, weight and condition of the patient to be treated; the route of administration; and the required regimen. Again, a physician will be able to determine the required route of administration and dosage for any particular patient. A typical daily dose may be from about 0.1 to 50 mg per kg, preferably from about 0.1mg/kg to 10mg/kg of body weight, according to the activity of the specific inhibitor, the age, weight and condition of the subject to be treated, and the frequency and route of administration. Preferably, daily dosage levels may be from 5 mg to 2 g.

A polynucleotide of the invention suitable for therapeutic use will also typically be formulated for administration with a pharmaceutically acceptable carrier or diluent. Such a polynucleotide may be administered by any known technique whereby expression of the desired polypeptide can be attained *in vivo*. For example, the polynucleotide may be introduced by injection, preferably intradermally, subcutaneously or intramuscularly. Alternatively, the nucleic acid may be delivered directly across the skin using a particle-mediated delivery device. A polynucleotide of the invention suitable for therapeutic nucleic acid may alternatively be administered to the oromucosal surface for example by intranasal or oral administration.

A non-viral vector of the invention suitable for therapeutic use may, for example, be packaged into liposomes or into surfactant containing vector delivery particles. Uptake of nucleic acid constructs of the invention may be enhanced by several known transfection techniques, for example those including the use of transfection agents. Examples of these agents include cationic agents, for example calcium phosphate and DEAE dextran and lipofectants, for example lipophectam and transfectam. The dosage of the nucleic acid to be administered can be varied. Typically, the nucleic acid will be administered in the range of from 1pg to 1mg, preferably from 1pg to 10μg nucleic acid for particle-mediated gene delivery and from 10μg to 1 mg for other routes.

Prediction of Type 1 interferon responsiveness

As also indicated above, in a still further aspect the present invention provides a method of predicting responsiveness of a patient to treatment with a Type 1 interferon, e.g. IFN-α treatment such as IFN-α treatment by an oromucosal route or intravenously, which comprises determining the level of HuIFRG 217.1 protein or a naturally-occurring variant thereof, or the corresponding mRNA, in a cell sample from said patient, wherein said sample is taken from said patient following administration of a Type 1 interferon or is treated prior to said determining with a Type 1 interferon *in vitro*.

Preferably, the Type 1 interferon for testing responsiveness will be the Type 1 interferon selected for treatment. It may be administered by the proposed treatment route and at the proposed treatment dose. Preferably, the subsequent sample analysed may be, for example, a blood sample or a sample of peripheral blood mononuclear cells (PBMCs) isolated from a blood sample.

More conveniently and preferably, a sample obtained from the patient comprising PBMCs isolated from blood may be treated *in vitro* with a Type 1 interferon, e.g. at a dosage range of about 1 to 10,000 IU/ml. Such treatment may be for a period of hours, e.g. about 7 to 8 hours. Preferred treatment conditions for such *in vitro* testing may be determined by testing PBMCs taken from normal donors with the same interferon and looking for upregulation of an appropriate expression product. Again, the Type 1 interferon employed will preferably be the Type 1 interferon proposed for treatment of the patient, e.g. recombinant IFN-α. PBMCs for such testing may be isolated in conventional manner from a blood sample using Ficoll-Hypaque density gradients. An example of a suitable protocol for such *in vitro* testing of Type 1 interferon responsiveness is provided in Example 3 below.

The sample, if appropriate after *in vitro* treatment with a Type 1 interferon, may be analysed for the level of HuIFRG 217.1 protein or a naturally-occurring variant thereof. This may be done using an antibody or antibodies capable of specifically binding one or more of HuIFRG 217.1 protein and naturally-occurring variants thereof, e.g. allelic variants thereof. Preferably, however, the sample will be analysed for mRNA encoding HuIFRG 217.1 protein or a naturally-occurring variant thereof. Such mRNA analysis may employ any of the techniques known for detection of mRNAs, e.g.

Northern blot detection or mRNA differential display. A variety of known nucleic acid amplification protocols may be employed to amplify any mRNA of interest present in the sample, or a portion thereof, prior to detection. The mRNA of interest, or a corresponding amplified nucleic acid, may be probed for using a nucleic acid probe attached to a solid support. Such a solid support may be a micro-array as previously discussed above carrying probes to determine the level of further mRNAs or amplification products thereof corresponding to Type 1 interferon upregulated genes, e.g. such genes identified as upregulated in response to oromucosal or intravenous administration of IFN-α.

The following examples illustrate the invention:

Examples

Example 1

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi 1987, (Anal. Biochem. **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α- ^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridize Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene) and cDNAs amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Isolation of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to

construct a human consensus sequence corresponding to a putative cDNA. One such cDNA was found to be 4,135 nucleotides in length. This corresponded to a mouse gene whose expression was found to be enhanced approximately 5-fold in the lymphoid tissue of the oral cavity of mice following oromucosal administration of recombinant murine IFN-α.

In order to establish that this putative cDNA corresponded to an authentic human gene, primers derived from the 5' and 3' ends of the consensus sequence were used to synthesise cDNA from mRNA extracted from human peripheral blood leukocytes (PBL) by specific reverse transcription and PCR amplification. A unique cDNA fragment of the predicted size was obtained, cloned and sequenced (SEQ. ID. No. 3). This human cDNA contains an open reading frame (ORF) of 1,857 bp in length at positions 36-1892 encoding a protein of 618 amino acids (SEQ. ID. No. 4). This transcript was named as HuIFRG 70.

Using this HuIFRG 70 sequence, a further cDNA named HuIFRG 217.1 was isolated by bioinformatics on the basis of sequence homology. The HuIFRG 70 sequence was compared with random human expressed sequence tags (EST) present in the dbEST database of Genbank of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to HuIFRG 70 were combined in a contig and used to construct a further human consensus sequence corresponding to a peutative cDNA. One such cDNA was found to be 8,157 nucleotides in length.

In order to establish that this peutative cDNA corresponded to an authentic human gene, primers derived from the 5′ and 3′ ends of the consensus sequence were used to synthesize cDNA from mRNA extracted from human peripheral blood leukocytes (PBL) by specific reverse transcription and PCR amplification. A unique cDNA fragment of the predicted size was obtained, cloned and sequenced (SEQ ID No. 1). This human cDNA contains an open reading frame (ORF) of 5,802 bp in length at positions 101 to 5900 encoding a protein of 1,933 amino acids (SEQ ID No. 2). This transcript was named as HuIFRG 217.1.

Example 2

Testing Type 1 interferon responsiveness *in vitro*

Human Daudi cells (a well characterized B lymphoblast cell line) were treated *in vitro* with 10,000 IU/ml of recombinant human IFN-α2 (Intron A from Schering-Plough) in PBS, with 1,000 IU/ml of recombinant IFN-γ or with an equal volume of PBS alone. Eight hours later the cells were centrifuged (800 x g for 10 minutes) and the cell pellet recovered. Total RNA was extracted from the cell pellet by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) 162,156-159) and 10.0 μg of total RNA per sample was subjected to Northern blotting in the presence of glyoxal and hybridised with a cDNA probe for HuIFRG 217.1 mRNA as described by Dandoy-Dron et al.(J. Biol. Chem. (1998) 273, 7691-7697). The blots were first exposed to autoradiography and then quantified using a Phospholmager according to the manufacturer's instructions. Enhanced levels of mRNA for HuIFRG 217.1 protein (approximately 5-fold) were detected in samples of RNA extracted from IFN-α and from IFN-γ treated cells compared to samples treated with PBS alone.

The same procedure may be used to predict Type 1 interferon responsiveness using peripheral blood mononuclear cells (PBMCs) taken from a patient proposed to be treated with a Type 1 interferon.

SEQUENCE LISTING

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tggcgcggcc cctgcagtcc ggcggagagc ggagctgagg atg gct gtg ccc ggc 115
Met Ala Val Pro Gly
1 5

tcc ttc ccg ctg ctg gtc gag ggc tcc tgg ggc ccc gac ccc ccg aag 163
Ser Phe Pro Leu Leu Val Glu Gly Ser Trp Gly Pro Asp Pro Pro Lys
10 15 20

aac ttg aac acc aag ttg cag atg tac ttc cag agc ccg aag agg tcg 211
Asn Leu Asn Thr Lys Leu Gln Met Tyr Phe Gln Ser Pro Lys Arg Ser
25 30 35

gga ggc ggc gag tgt gag gtc cgc cag gat ccc agg agc cca tcc cgc 259
Gly Gly Gly Glu Cys Glu Val Arg Gln Asp Pro Arg Ser Pro Ser Arg
40 45 50

ttc ctg gtg ttc ttc tac ccg gag gac ggg aaa tgg cgg cag ggc acg 307
Phe Leu Val Phe Phe Tyr Pro Glu Asp Gly Lys Trp Arg Gln Gly Thr
55 60 65

cac ggg agg gtg acc cgc ccg act tcg gcg gct gct gta gcg gag gcg 355
His Gly Arg Val Thr Arg Pro Thr Ser Ala Ala Ala Val Ala Glu Ala
70 75 80 85

ctt aat ggc gcg gcc cgg agg tgg cgg cgg aac cgc gca agt aac tct 403
Leu Asn Gly Ala Ala Arg Arg Trp Arg Arg Asn Arg Ala Ser Asn Ser
90 95 100

tta tcc ctc gat cgt ttt ctg tct ttc cct gtt gtg gtg gtg tta ttg 451
Leu Ser Leu Asp Arg Phe Leu Ser Phe Pro Val Val Val Val Leu Leu
105 110 115

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ctg tct ttt cct gtt gtt att att ctt gtg tgg gga agg aaa ctg att      547
Leu Ser Phe Pro Val Val Ile Ile Leu Val Trp Gly Arg Lys Leu Ile
    135                 140                 145

aag aaa cgt ggc aag tca cag aga ttc ctt gtg gtt ctt gga gat tcc      595
Lys Lys Arg Gly Lys Ser Gln Arg Phe Leu Val Val Leu Gly Asp Ser
150                 155                 160                 165

cag ggg tcc cgg ggt cac ttg gga gag ggg cag agg cgc tac cta aaa      643
Gln Gly Ser Arg Gly His Leu Gly Glu Gly Gln Arg Arg Tyr Leu Lys
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tca cac tgc ctg aat gtc aac gta gag ccg tca cag cgg cca cat tgg      691
Ser His Cys Leu Asn Val Asn Val Glu Pro Ser Gln Arg Pro His Trp
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agg ggc tgt cga tcg acc aca gtt cgg cag aag gtt ctg gag aga aaa      739
Arg Gly Cys Arg Ser Thr Thr Val Arg Gln Lys Val Leu Glu Arg Lys
        200                 205                 210

aat cat gag ttg gta tgg caa gga aaa gga aca ttc aag tta act gtc      787
Asn His Glu Leu Val Trp Gln Gly Lys Gly Thr Phe Lys Leu Thr Val
    215                 220                 225

cag tta cct gca acc cca gat gaa atc gat cat gtc ttt gaa gag gaa      835
Gln Leu Pro Ala Thr Pro Asp Glu Ile Asp His Val Phe Glu Glu Glu
230                 235                 240                 245

ctt cta aca aaa gca aat gtg tca gaa gaa ttg gat aca aaa ctc cct      883
Leu Leu Thr Lys Ala Asn Val Ser Glu Glu Leu Asp Thr Lys Leu Pro
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ctt gat ggt gga tta gac aaa atg gaa gat atc cca gag gaa tgt gaa      931
Leu Asp Gly Gly Leu Asp Lys Met Glu Asp Ile Pro Glu Glu Cys Glu
            265                 270                 275

aat att tcc tct ttg gtg gca ttt gaa aac ctc aag gca aat gtg act      979
Asn Ile Ser Ser Leu Val Ala Phe Glu Asn Leu Lys Ala Asn Val Thr
        280                 285                 290

gac ata atg cta atc ttg tta gtg gag aac ata agt ggc ctg tct aat     1027
Asp Ile Met Leu Ile Leu Leu Val Glu Asn Ile Ser Gly Leu Ser Asn
    295                 300                 305

gat gac ttt caa gtg gaa ata ata aga gat ttt gat gtt gct gtt gtt     1075
Asp Asp Phe Gln Val Glu Ile Ile Arg Asp Phe Asp Val Ala Val Val
310                 315                 320                 325

acc ttt caa aag cac ata gat act ata aga ttt gtt gat gat tgt acc     1123
Thr Phe Gln Lys His Ile Asp Thr Ile Arg Phe Val Asp Asp Cys Thr
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Lys His His Ser Ile Lys Gln Leu Gln Leu Ser Pro Arg Leu Leu Glu
            345                 350                 355

gtg aca aac aca atc agg gtt gaa aac ctg cca cct ggt gct gat gac     1219
Val Thr Asn Thr Ile Arg Val Glu Asn Leu Pro Pro Gly Ala Asp Asp
        360                 365                 370

tac agt tta aaa ctt ttc ttt gaa aat ccc tat aat gga ggg gga aga     1267
Tyr Ser Leu Lys Leu Phe Phe Glu Asn Pro Tyr Asn Gly Gly Gly Arg
    375                 380                 385

gtt gcc aat gtt gaa tat ttt cct gaa gag agt tca gct ctg att gaa     1315
Val Ala Asn Val Glu Tyr Phe Pro Glu Glu Ser Ser Ala Leu Ile Glu
390                 395                 400                 405

ttt ttt gac aga aaa gtg tta gac acc atc atg gcc aca aaa ctc gac     1363
Phe Phe Asp Arg Lys Val Leu Asp Thr Ile Met Ala Thr Lys Leu Asp
                410                 415                 420

ttc aat aaa atg cca ctt tct gtg ttc cca tac tat gcc tca ttg ggc     1411
Phe Asn Lys Met Pro Leu Ser Val Phe Pro Tyr Tyr Ala Ser Leu Gly
            425                 430                 435

aca gcc ttg tat gga aag gag aag cct ctg atc aag ctt cca gca cca     1459
Thr Ala Leu Tyr Gly Lys Glu Lys Pro Leu Ile Lys Leu Pro Ala Pro
        440                 445                 450

ttt gaa gag tca cta gat ctt ccc tta tgg aag ttc tta cag aaa aag     1507
Phe Glu Glu Ser Leu Asp Leu Pro Leu Trp Lys Phe Leu Gln Lys Lys
    455                 460                 465

aat cac ctc att gag gag ata aac gat gaa atg agg cgt tgt cac tgt     1555
Asn His Leu Ile Glu Glu Ile Asn Asp Glu Met Arg Arg Cys His Cys
470                 475                 480                 485

gag ctc acg tgg tcc caa ctc agt ggt aaa gtt acc atc aga cca gca     1603
Glu Leu Thr Trp Ser Gln Leu Ser Gly Lys Val Thr Ile Arg Pro Ala
                490                 495                 500

gcc acc tta gtc aat gaa gga aga ccg aga atc aag acc tgg cag gca     1651
Ala Thr Leu Val Asn Glu Gly Arg Pro Arg Ile Lys Thr Trp Gln Ala
            505                 510                 515

gat act tcc aca aca ctc tct agc atc agg tct aaa tat aaa gtc aac     1699
Asp Thr Ser Thr Thr Leu Ser Ser Ile Arg Ser Lys Tyr Lys Val Asn
        520                 525                 530

cca att aaa gtg gat cca aca atg tgg gac acc ata aaa aat gat gtg     1747
Pro Ile Lys Val Asp Pro Thr Met Trp Asp Thr Ile Lys Asn Asp Val
    535                 540                 545

aaa gat gac agg att ttg att gag ttt gat aca ctt aag gag atg gta     1795
Lys Asp Asp Arg Ile Leu Ile Glu Phe Asp Thr Leu Lys Glu Met Val
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atc tta gca ggg aaa tca gag gat gtc caa agc att gag gta caa gtc     1843
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agg gag tta ata gaa agc act act caa aaa att aaa agg gaa gag caa     1891
Arg Glu Leu Ile Glu Ser Thr Thr Gln Lys Ile Lys Arg Glu Glu Gln
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agt ttg aag gaa aaa atg atc att tct cca ggc agg tat ttt ctt ttg     1939
Ser Leu Lys Glu Lys Met Ile Ile Ser Pro Gly Arg Tyr Phe Leu Leu
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tgt cac agc agt cta ctg gac cat tta ctc acg gag tgc cca gag ata     1987
Cys His Ser Ser Leu Leu Asp His Leu Leu Thr Glu Cys Pro Glu Ile
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        680                 685                 690

cag aag att ctt gca ctt tat gag cta gag ggt aca act gtt ctc tta     2227
Gln Lys Ile Leu Ala Leu Tyr Glu Leu Glu Gly Thr Thr Val Leu Leu
    695                 700                 705

acc agc tgt tct tct gaa gcc ctg tta gaa gca gaa aag caa atg ctc     2275
Thr Ser Cys Ser Ser Glu Ala Leu Leu Glu Ala Glu Lys Gln Met Leu
710                 715                 720                 725

agt gcc tta aat tat aag cgc att gaa gtt gag aac aaa gaa gtt ctt     2323
Ser Ala Leu Asn Tyr Lys Arg Ile Glu Val Glu Asn Lys Glu Val Leu
                730                 735                 740

cat ggc aag aaa tgg aaa ggg ctc act cac aat ttg ctt aag aaa caa     2371
His Gly Lys Lys Trp Lys Gly Leu Thr His Asn Leu Leu Lys Lys Gln
            745                 750                 755

aat tcc tcc cca aac act gta atc atc aat gag tta act tca gaa acc     2419
Asn Ser Ser Pro Asn Thr Val Ile Ile Asn Glu Leu Thr Ser Glu Thr
        760                 765                 770

aca gct gaa gtc atc att aca ggc tgt gta aaa gaa gta aat gaa acc     2467
Thr Ala Glu Val Ile Ile Thr Gly Cys Val Lys Glu Val Asn Glu Thr
    775                 780                 785
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tat aaa ttg ctt ttt aac ttc gtt gaa caa aac atg aaa ata gag aga     2515
Tyr Lys Leu Leu Phe Asn Phe Val Glu Gln Asn Met Lys Ile Glu Arg
790                 795                 800                 805

ctg gtt gaa gta aag cct tcc tta gtt att gac tat tta aag aca gaa     2563
Leu Val Glu Val Lys Pro Ser Leu Val Ile Asp Tyr Leu Lys Thr Glu
                810                 815                 820

aag aag cta ttc tgg cca aag ata aag aag gta aat gtg cag gta agt     2611
Lys Lys Leu Phe Trp Pro Lys Ile Lys Lys Val Asn Val Gln Val Ser
            825                 830                 835

ttc aat cct gag aac aaa caa aaa ggc att tta cta act ggc tca aag     2659
Phe Asn Pro Glu Asn Lys Gln Lys Gly Ile Leu Leu Thr Gly Ser Lys
        840                 845                 850

acc gaa gta ctg aag gca gtg gac att gtc aag caa gtc tgg gat tca     2707
Thr Glu Val Leu Lys Ala Val Asp Ile Val Lys Gln Val Trp Asp Ser
    855                 860                 865

gtc tgt gtt aaa agt gtc cat act gat aag cca gga gcc aag cag ttc     2755
Val Cys Val Lys Ser Val His Thr Asp Lys Pro Gly Ala Lys Gln Phe
870                 875                 880                 885

ttc cag gat aaa gca cgg ttt tat caa agt gag atc aaa cgg ttg ttt     2803
Phe Gln Asp Lys Ala Arg Phe Tyr Gln Ser Glu Ile Lys Arg Leu Phe
                890                 895                 900

ggt tgt tac att gaa cta cag gag aat gaa gta atg aag gag gga ggc     2851
Gly Cys Tyr Ile Glu Leu Gln Glu Asn Glu Val Met Lys Glu Gly Gly
            905                 910                 915

agc ccc gct ggg cag aag tgc ttc tct cgg aca gtc ttg gcc cct ggc     2899
Ser Pro Ala Gly Gln Lys Cys Phe Ser Arg Thr Val Leu Ala Pro Gly
        920                 925                 930

gtt gtg ctg att gtg cag cag ggt gac ttg gca cgg ctt cct gtc gat     2947
Val Val Leu Ile Val Gln Gln Gly Asp Leu Ala Arg Leu Pro Val Asp
    935                 940                 945

gtg gtg gtg aat gca tct aat gag gac ctt aag cat tat ggt ggc ctg     2995
Val Val Val Asn Ala Ser Asn Glu Asp Leu Lys His Tyr Gly Gly Leu
950                 955                 960                 965

gcc gct gcg ctc tca aaa gca gct ggc cct gag ctc cag gcc gac tgt     3043
Ala Ala Ala Leu Ser Lys Ala Ala Gly Pro Glu Leu Gln Ala Asp Cys
                970                 975                 980

gac cag ata gtg aag aga gag ggc aga ctc cta ccg ggc aat gcc acc     3091
Asp Gln Ile Val Lys Arg Glu Gly Arg Leu Leu Pro Gly Asn Ala Thr
            985                 990                 995

atc tcc aag  gca gga aag ctg ccc  tac cac cac gtg atc  cat gca     3136
Ile Ser Lys  Ala Gly Lys Leu Pro  Tyr His His Val Ile  His Ala
        1000                1005                1010
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gtg ggg ccc  cgc tgg agc gga tat  gag gcc ccg agg tgt  gtg tac      3181
Val Gly Pro  Arg Trp Ser Gly Tyr  Glu Ala Pro Arg Cys  Val Tyr
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cta tta agg  aga gct gtg caa ctc  agt ctc tgt cta gcc  gaa aaa      3226
Leu Leu Arg  Arg Ala Val Gln Leu  Ser Leu Cys Leu Ala  Glu Lys
        1030                 1035                 1040

tac aag tac  cga tcc ata gcc atc  cca gct att agt tct  gga gtc      3271
Tyr Lys Tyr  Arg Ser Ile Ala Ile  Pro Ala Ile Ser Ser  Gly Val
        1045                 1050                 1055

ttt ggc ttt  ccc tta ggc cga tgc  gtg gag acc att gtt  tct gcc      3316
Phe Gly Phe  Pro Leu Gly Arg Cys  Val Glu Thr Ile Val  Ser Ala
        1060                 1065                 1070

atc aag gaa  aac ttc caa ttc aag  aag gat gga cac tgc  ttg aaa      3361
Ile Lys Glu  Asn Phe Gln Phe Lys  Lys Asp Gly His Cys  Leu Lys
        1075                 1080                 1085

gaa atc tac  ctt gtg gat gta tct  gag aag act gtt gag  gcc ttt      3406
Glu Ile Tyr  Leu Val Asp Val Ser  Glu Lys Thr Val Glu  Ala Phe
        1090                 1095                 1100

gca gaa gct  gtg aaa act gta ttt  aaa gcc acc ctg cca  gat aca      3451
Ala Glu Ala  Val Lys Thr Val Phe  Lys Ala Thr Leu Pro  Asp Thr
        1105                 1110                 1115

gct gcc ccg  cca ggt tta cca cca  gca gca gcg ggg cct  ggg aaa      3496
Ala Ala Pro  Pro Gly Leu Pro Pro  Ala Ala Ala Gly Pro  Gly Lys
        1120                 1125                 1130

aca tca tgg  gaa aaa gga agc ctg  gtg tcc ccg gga ggc  ctg cag      3541
Thr Ser Trp  Glu Lys Gly Ser Leu  Val Ser Pro Gly Gly  Leu Gln
        1135                 1140                 1145

atg ctg ttg  gtg aaa gag ggt gtg  cag aat gct aag acc  gat gtt      3586
Met Leu Leu  Val Lys Glu Gly Val  Gln Asn Ala Lys Thr  Asp Val
        1150                 1155                 1160

gtt gtc aac  tcc gtt ccc ttg gat  ctc gtg ctt agt aga  ggg cct      3631
Val Val Asn  Ser Val Pro Leu Asp  Leu Val Leu Ser Arg  Gly Pro
        1165                 1170                 1175

ctt tct aag  tcc ctc ttg gaa aaa  gct gga cca gag ctc  cag gag      3676
Leu Ser Lys  Ser Leu Leu Glu Lys  Ala Gly Pro Glu Leu  Gln Glu
        1180                 1185                 1190

gaa ttg gac  aca gtt gga caa ggg  gtg gct gtc agc atg  ggc aca      3721
Glu Leu Asp  Thr Val Gly Gln Gly  Val Ala Val Ser Met  Gly Thr
        1195                 1200                 1205

gtg ctc aaa  acc agc agc tgg aat  ctg gac tgt cgc tat  gtg ctt      3766
Val Leu Lys  Thr Ser Ser Trp Asn  Leu Asp Cys Arg Tyr  Val Leu
        1210                 1215                 1220
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cac gtg gta  gct ccg gag tgg aga  aat ggt agc aca tct  tca ctc      3811
His Val Val  Ala Pro Glu Trp Arg  Asn Gly Ser Thr Ser  Ser Leu
        1225                 1230                 1235

aag ata atg  gaa gac ata atc aga  gaa tgt atg gag atc  act gag      3856
Lys Ile Met  Glu Asp Ile Ile Arg  Glu Cys Met Glu Ile  Thr Glu
        1240                 1245                 1250

agc ttg tcc  tta aaa tca att gca  ttt cca gca ata gga  aca gga      3901
Ser Leu Ser  Leu Lys Ser Ile Ala  Phe Pro Ala Ile Gly  Thr Gly
        1255                 1260                 1265

aac ttg gga  ttt cct aaa aac ata  ttc gct gaa tta atc  att tca      3946
Asn Leu Gly  Phe Pro Lys Asn Ile  Phe Ala Glu Leu Ile  Ile Ser
        1270                 1275                 1280

gag gtg ttc  aaa ttt agt agc aag  aat cag ctg aaa act  tta caa      3991
Glu Val Phe  Lys Phe Ser Ser Lys  Asn Gln Leu Lys Thr  Leu Gln
        1285                 1290                 1295

gag gtt cac  ttt ctg ctg cac ccg  agt gat cat gaa aat  att cag      4036
Glu Val His  Phe Leu Leu His Pro  Ser Asp His Glu Asn  Ile Gln
        1300                 1305                 1310

gca ttt tca  gat gaa ttt gcc aga  agg gct aat gga aat  ctc gtc      4081
Ala Phe Ser  Asp Glu Phe Ala Arg  Arg Ala Asn Gly Asn  Leu Val
        1315                 1320                 1325

agt gac aaa  att ccg aag gct aaa  gat aca caa ggt ttt  tat ggg      4126
Ser Asp Lys  Ile Pro Lys Ala Lys  Asp Thr Gln Gly Phe  Tyr Gly
        1330                 1335                 1340

act gtt tct  agc cct gat tca ggt  gtg tat gaa atg aag  att ggc      4171
Thr Val Ser  Ser Pro Asp Ser Gly  Val Tyr Glu Met Lys  Ile Gly
        1345                 1350                 1355

tcc atc atc  ttc cag gtg gct tct  gga gat atc acg aaa  gaa gag      4216
Ser Ile Ile  Phe Gln Val Ala Ser  Gly Asp Ile Thr Lys  Glu Glu
        1360                 1365                 1370

aca gat gtg  att gta aat tca aca  tca aac tca ttc aat  ctc aaa      4261
Thr Asp Val  Ile Val Asn Ser Thr  Ser Asn Ser Phe Asn  Leu Lys
        1375                 1380                 1385

gca ggg gtc  tcc aaa gca att tta  gaa tgt gct gga caa  aat gta      4306
Ala Gly Val  Ser Lys Ala Ile Leu  Glu Cys Ala Gly Gln  Asn Val
        1390                 1395                 1400

gaa agg gaa  tgt tct cag caa gct  cag cag cgc aaa aat  gat tat      4351
Glu Arg Glu  Cys Ser Gln Gln Ala  Gln Gln Arg Lys Asn  Asp Tyr
        1405                 1410                 1415

ata atc acc  gga ggt gga ttt ttg  agg tgc aag aat atc  att cat      4396
Ile Ile Thr  Gly Gly Gly Phe Leu  Arg Cys Lys Asn Ile  Ile His
        1420                 1425                 1430
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gta att ggt  gga aat gat gtc aag  agt tca gtt tcc tct  gtt ttg      4441
Val Ile Gly  Gly Asn Asp Val Lys  Ser Ser Val Ser Ser  Val Leu
        1435                 1440                 1445

cag gag tgt  gaa aaa aaa aat tac  tca tcc att tgc ctc  cca gcc      4486
Gln Glu Cys  Glu Lys Lys Asn Tyr  Ser Ser Ile Cys Leu  Pro Ala
        1450                 1455                 1460

att ggg aca  gga aat gcc aaa caa  cac cca gat aag gtt  gct gaa      4531
Ile Gly Thr  Gly Asn Ala Lys Gln  His Pro Asp Lys Val  Ala Glu
        1465                 1470                 1475

gcc ata att  gat gcc att gaa gac  ttt gtc cag aaa gga  tca gcc      4576
Ala Ile Ile  Asp Ala Ile Glu Asp  Phe Val Gln Lys Gly  Ser Ala
        1480                 1485                 1490

cag tct gtg  aaa aaa gtt aaa gtt  gtt atc ttt ctg cct  caa gta      4621
Gln Ser Val  Lys Lys Val Lys Val  Val Ile Phe Leu Pro  Gln Val
        1495                 1500                 1505

ctg gat gtg  ttt tat gcc aac atg  aag aaa aga gaa ggg  act cag      4666
Leu Asp Val  Phe Tyr Ala Asn Met  Lys Lys Arg Glu Gly  Thr Gln
        1510                 1515                 1520

ctt tct tcc  caa cag tct gtg atg  tct aaa ctt gca tca  ttt ttg      4711
Leu Ser Ser  Gln Gln Ser Val Met  Ser Lys Leu Ala Ser  Phe Leu
        1525                 1530                 1535

ggc ttt tca  aag caa tct ccc caa  aaa aag aat cat ttg  gtt ttg      4756
Gly Phe Ser  Lys Gln Ser Pro Gln  Lys Lys Asn His Leu  Val Leu
        1540                 1545                 1550

gaa aag aaa  aca gaa tca gca act  ttt cgg gtg tgt ggt  gaa aat      4801
Glu Lys Lys  Thr Glu Ser Ala Thr  Phe Arg Val Cys Gly  Glu Asn
        1555                 1560                 1565

gtc acg tgt  gtg gaa tat gct atc  tcc tgg cta caa gac  ctg att      4846
Val Thr Cys  Val Glu Tyr Ala Ile  Ser Trp Leu Gln Asp  Leu Ile
        1570                 1575                 1580

gaa aaa gaa  cag tgt cct tac acc  agt gaa gat gag tgc  atc aaa      4891
Glu Lys Glu  Gln Cys Pro Tyr Thr  Ser Glu Asp Glu Cys  Ile Lys
        1585                 1590                 1595

gac ttt gat  gaa aag gag tat cag  gag ttg aat gag ctg  cag aag      4936
Asp Phe Asp  Glu Lys Glu Tyr Gln  Glu Leu Asn Glu Leu  Gln Lys
        1600                 1605                 1610

aag tta aat  att aac att tcc ctg  gac cat aag aga cct  ttg att      4981
Lys Leu Asn  Ile Asn Ile Ser Leu  Asp His Lys Arg Pro  Leu Ile
        1615                 1620                 1625

aag gtt ttg  gga att agc aga gat  gtg atg cag gct aga  gat gaa      5026
Lys Val Leu  Gly Ile Ser Arg Asp  Val Met Gln Ala Arg  Asp Glu
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att gag gcg  atg atc aag aga gtt  cga ttg gcc aaa gaa  cag gaa      5071
Ile Glu Ala  Met Ile Lys Arg Val  Arg Leu Ala Lys Glu  Gln Glu
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tcc cgg gca  gat tgt atc agt gag  ttt ata gaa tgg cag  tat aat      5116
Ser Arg Ala  Asp Cys Ile Ser Glu  Phe Ile Glu Trp Gln  Tyr Asn
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gac aat aac  act tct cat tgt ttt  aac aaa atg acc aat  ctg aaa      5161
Asp Asn Asn  Thr Ser His Cys Phe  Asn Lys Met Thr Asn  Leu Lys
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tta gag gat  gca agg aga gaa aag  aaa aaa aca gtt gat  gtc aaa      5206
Leu Glu Asp  Ala Arg Arg Glu Lys  Lys Lys Thr Val Asp  Val Lys
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att aat cat  cgg cac tac aca gtg  aac ttg aac aca tac  act gcc      5251
Ile Asn His  Arg His Tyr Thr Val  Asn Leu Asn Thr Tyr  Thr Ala
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aca gac aca  aag ggc cac agt tta  tct gtt cag cgc ctc  acg aaa      5296
Thr Asp Thr  Lys Gly His Ser Leu  Ser Val Gln Arg Leu  Thr Lys
       1720                1725                1730

tcc aaa gtt  gac atc cct gca cac  tgg agt gat atg aag  cag cag      5341
Ser Lys Val  Asp Ile Pro Ala His  Trp Ser Asp Met Lys  Gln Gln
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aat ttc tgt  gtg gtg gag ctg ctg  cct agt gat cct gag  tac aac      5386
Asn Phe Cys  Val Val Glu Leu Leu  Pro Ser Asp Pro Glu  Tyr Asn
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acg gtg gca  agc aag ttt aat cag  acc tgc tca cac ttc  aga ata      5431
Thr Val Ala  Ser Lys Phe Asn Gln  Thr Cys Ser His Phe  Arg Ile
       1765                1770                1775

gag aag att  gag agg atc cag aat  cca gat ctc tgg aat  agc tac      5476
Glu Lys Ile  Glu Arg Ile Gln Asn  Pro Asp Leu Trp Asn  Ser Tyr
       1780                1785                1790

cag gca aag  aaa aaa act atg gat  gcc aag aat ggc cag  aca atg      5521
Gln Ala Lys  Lys Lys Thr Met Asp  Ala Lys Asn Gly Gln  Thr Met
       1795                1800                1805

aat gag aag  caa ctc ttc cat ggg  aca gat gcc ggc tcc  gtg cca      5566
Asn Glu Lys  Gln Leu Phe His Gly  Thr Asp Ala Gly Ser  Val Pro
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cac gtc aat  cga aat ggc ttt aac  cgc agc tat gcc gga  aag aat      5611
His Val Asn  Arg Asn Gly Phe Asn  Arg Ser Tyr Ala Gly  Lys Asn
       1825                1830                1835

gct gtg gca  tat gga aag gga acc  tat ttt gct gtc aat  gcc aat      5656
Ala Val Ala  Tyr Gly Lys Gly Thr  Tyr Phe Ala Val Asn  Ala Asn
       1840                1845                1850
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tat tct gcc  aat gat acg tac tcc  aga cca gat gca aat  ggg aga      5701
Tyr Ser Ala  Asn Asp Thr Tyr Ser  Arg Pro Asp Ala Asn  Gly Arg
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aag cat gtg  tat tat gtg cga gta  ctt act gga atc tat  aca cat      5746
Lys His Val  Tyr Tyr Val Arg Val  Leu Thr Gly Ile Tyr  Thr His
        1870                 1875                 1880

gga aat cat  tca tta att gtg cct  cct tca aag aac cct  caa aat      5791
Gly Asn His  Ser Leu Ile Val Pro  Pro Ser Lys Asn Pro  Gln Asn
        1885                 1890                 1895

cct act gac  ctg tat gac act gtc  aca gat aat gtg cac  cat cca      5836
Pro Thr Asp  Leu Tyr Asp Thr Val  Thr Asp Asn Val His  His Pro
        1900                 1905                 1910

agt tta ttt  gtg gca ttt tat gac  tac caa gca tac cca  gag tac      5881
Ser Leu Phe  Val Ala Phe Tyr Asp  Tyr Gln Ala Tyr Pro  Glu Tyr
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ctt att acg  ttt aga aaa taa cactttggta tccttcccac aaaattattc      5932
Leu Ile Thr  Phe Arg Lys
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        35                  40                  45

Arg Ser Pro Ser Arg Phe Leu Val Phe Phe Tyr Pro Glu Asp Gly Lys
    50                  55                  60

Trp Arg Gln Gly Thr His Gly Arg Val Thr Arg Pro Thr Ser Ala Ala
65                  70                  75                  80

Ala Val Ala Glu Ala Leu Asn Gly Ala Ala Arg Arg Trp Arg Arg Asn
                85                  90                  95

Arg Ala Ser Asn Ser Leu Ser Leu Asp Arg Phe Leu Ser Phe Pro Val
            100                 105                 110

Val Val Val Leu Leu Phe Val Val Val Val Val Glu Val Ser Leu Ser
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Ser Tyr His Pro Phe Leu Ser Phe Pro Val Val Ile Ile Leu Val Trp
    130                 135                 140

Gly Arg Lys Leu Ile Lys Lys Arg Gly Lys Ser Gln Arg Phe Leu Val
145                 150                 155                 160

Val Leu Gly Asp Ser Gln Gly Ser Arg Gly His Leu Gly Glu Gly Gln
                165                 170                 175

Arg Arg Tyr Leu Lys Ser His Cys Leu Asn Val Asn Val Glu Pro Ser
            180                 185                 190

Gln Arg Pro His Trp Arg Gly Cys Arg Ser Thr Thr Val Arg Gln Lys
        195                 200                 205

Val Leu Glu Arg Lys Asn His Glu Leu Val Trp Gln Gly Lys Gly Thr
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Phe Lys Leu Thr Val Gln Leu Pro Ala Thr Pro Asp Glu Ile Asp His
225                 230                 235                 240

Val Phe Glu Glu Glu Leu Leu Thr Lys Ala Asn Val Ser Glu Glu Leu
                245                 250                 255

Asp Thr Lys Leu Pro Leu Asp Gly Gly Leu Asp Lys Met Glu Asp Ile
            260                 265                 270

Pro Glu Glu Cys Glu Asn Ile Ser Ser Leu Val Ala Phe Glu Asn Leu
        275                 280                 285

Lys Ala Asn Val Thr Asp Ile Met Leu Ile Leu Leu Val Glu Asn Ile
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Ser Gly Leu Ser Asn Asp Asp Phe Gln Val Glu Ile Ile Arg Asp Phe
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Pro Gly Ala Asp Asp Tyr Ser Leu Lys Leu Phe Phe Glu Asn Pro Tyr
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Asn Gly Gly Gly Arg Val Ala Asn Val Glu Tyr Phe Pro Glu Glu Ser
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Ser Ala Leu Ile Glu Phe Phe Asp Arg Lys Val Leu Asp Thr Ile Met
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Ala Thr Lys Leu Asp Phe Asn Lys Met Pro Leu Ser Val Phe Pro Tyr
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Tyr Ala Ser Leu Gly Thr Ala Leu Tyr Gly Lys Glu Lys Pro Leu Ile
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Ile Lys Asn Asp Val Lys Asp Asp Arg Ile Leu Ile Glu Phe Asp Thr
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Leu Lys Glu Met Val Ile Leu Ala Gly Lys Ser Glu Asp Val Gln Ser
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Ile Glu Val Gln Val Arg Glu Leu Ile Glu Ser Thr Thr Gln Lys Ile
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Lys Arg Glu Glu Gln Ser Leu Lys Glu Lys Met Ile Ile Ser Pro Gly
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Arg Tyr Phe Leu Leu Cys His Ser Ser Leu Leu Asp His Leu Leu Thr
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Glu Cys Pro Glu Ile Glu Ile Cys Tyr Asp Arg Val Thr Gln His Leu
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Cys Leu Lys Gly Pro Ser Ala Asp Val Tyr Lys Ala Lys Cys Glu Ile
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Gln Glu Lys Val Tyr Thr Met Ala Gln Lys Asn Ile Gln Val Ser Pro
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Cys Leu Phe Ile Ala Gln Lys Ile Leu Ala Leu Tyr Glu Leu Glu Gly
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Asn Lys Glu Val Leu His Gly Lys Lys Trp Lys Gly Leu Thr His Asn
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Leu Leu Lys Lys Gln Asn Ser Ser Pro Asn Thr Val Ile Ile Asn Glu
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Leu Thr Ser Glu Thr Thr Ala Glu Val Ile Ile Thr Gly Cys Val Lys
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Tyr Leu Lys Thr Glu Lys Lys Leu Phe Trp Pro Lys Ile Lys Lys Val
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Asn Val Gln Val Ser Phe Asn Pro Glu Asn Lys Gln Lys Gly Ile Leu
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Met Lys Glu Gly Gly Ser Pro Ala Gly Gln Lys Cys Phe Ser Arg Thr
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Arg Leu Pro Val Asp Val Val Val Asn Ala Ser Asn Glu Asp Leu Lys
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His Tyr Gly Gly Leu Ala Ala Ala Leu Ser Lys Ala Ala Gly Pro Glu
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Leu Gln Ala Asp Cys Asp Gln Ile Val Lys Arg Glu Gly Arg Leu Leu
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Pro Gly Asn Ala Thr Ile Ser Lys Ala Gly Lys Leu Pro Tyr His His
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Leu Ala Glu Lys Tyr Lys Tyr Arg Ser Ile Ala Ile Pro Ala Ile
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Ser Ser Gly Val Phe Gly Phe Pro Leu Gly Arg Cys Val Glu Thr
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Ile Val Ser Ala Ile Lys Glu Asn Phe Gln Phe Lys Lys Asp Gly
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Val Glu Ala Phe Ala Glu Ala Val Lys Thr Val Phe Lys Ala Thr
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Leu Pro Asp Thr Ala Ala Pro Pro Gly Leu Pro Pro Ala Ala Ala
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Gly Gly Leu Gln Met Leu Leu Val Lys Glu Gly Val Gln Asn Ala
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Lys Thr Asp Val Val Val Asn Ser Val Pro Leu Asp Leu Val Leu
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Thr Ser Ser Leu Lys Ile Met Glu Asp Ile Ile Arg Glu Cys Met
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Glu Ile Thr Glu Ser Leu Ser Leu Lys Ser Ile Ala Phe Pro Ala
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Ile Gly Thr Gly Asn Leu Gly Phe Pro Lys Asn Ile Phe Ala Glu
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Gly Phe Tyr Gly Thr Val Ser Ser Pro Asp Ser Gly Val Tyr Glu
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Thr Lys Glu Glu Thr Asp Val Ile Val Asn Ser Thr Ser Asn Ser
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Phe Asn Leu Lys Ala Gly Val Ser Lys Ala Ile Leu Glu Cys Ala
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Lys Asn Asp Tyr Ile Ile Thr Gly Gly Gly Phe Leu Arg Cys Lys
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Asn Ile Ile His Val Ile Gly Gly Asn Asp Val Lys Ser Ser Val
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His Leu Val Leu Glu Lys Lys Thr Glu Ser Ala Thr Phe Arg Val
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Lys Glu Gln Glu Ser Arg Ala Asp Cys Ile Ser Glu Phe Ile Glu
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Trp Gln Tyr Asn Asp Asn Asn Thr Ser His Cys Phe Asn Lys Met
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Val Asp Val Lys Ile Asn His Arg His Tyr Thr Val Asn Leu Asn
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Thr Tyr Thr Ala Thr Asp Thr Lys Gly His Ser Leu Ser Val Gln
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Arg Leu Thr Lys Ser Lys Val Asp Ile Pro Ala His Trp Ser Asp
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Met Lys Gln Gln Asn Phe Cys Val Val Glu Leu Leu Pro Ser Asp
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Pro Glu Tyr Asn Thr Val Ala Ser Lys Phe Asn Gln Thr Cys Ser
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His Phe Arg Ile Glu Lys Ile Glu Arg Ile Gln Asn Pro Asp Leu
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Trp Asn Ser Tyr Gln Ala Lys Lys Lys Thr Met Asp Ala Lys Asn
1790 1795 1800

Gly Gln Thr Met Asn Glu Lys Gln Leu Phe His Gly Thr Asp Ala
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Gly Ser Val Pro His Val Asn Arg Asn Gly Phe Asn Arg Ser Tyr
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Ala Gly Lys Asn Ala Val Ala Tyr Gly Lys Gly Thr Tyr Phe Ala
1835 1840 1845

Val Asn Ala Asn Tyr Ser Ala Asn Asp Thr Tyr Ser Arg Pro Asp
1850 1855 1860

Ala Asn Gly Arg Lys His Val Tyr Tyr Val Arg Val Leu Thr Gly
1865 1870 1875

Ile Tyr Thr His Gly Asn His Ser Leu Ile Val Pro Pro Ser Lys
1880 1885 1890

Asn Pro Gln Asn Pro Thr Asp Leu Tyr Asp Thr Val Thr Asp Asn
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1925 1930

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Val Lys Glu Asn Leu Val Ser Asp Lys Phe Pro Lys Ala Lys Asp Thr
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caa ggt ttt tat ggg act gtt tct agc cct gat tca ggt gtg tat gaa      149
Gln Gly Phe Tyr Gly Thr Val Ser Ser Pro Asp Ser Gly Val Tyr Glu
       25                  30                  35

atg aag att ggc tcc atc atc ttc cag gtg gct tct gga gat atc acg      197
Met Lys Ile Gly Ser Ile Ile Phe Gln Val Ala Ser Gly Asp Ile Thr
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aaa gaa gag gca gat gtg att gta aat tca aca tca aac tca ttc aat      245
Lys Glu Glu Ala Asp Val Ile Val Asn Ser Thr Ser Asn Ser Phe Asn
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ctc aaa gca ggg gtc tcc aaa gca att tta gaa tgt gct gga caa aat      293
Leu Lys Ala Gly Val Ser Lys Ala Ile Leu Glu Cys Ala Gly Gln Asn
               75                  80                  85

gta gaa agg gaa tgt tct cag caa gct cag cag cgc aaa aat gat tat      341
Val Glu Arg Glu Cys Ser Gln Gln Ala Gln Gln Arg Lys Asn Asp Tyr
          90                  95                  100

ata atc acc gga ggt gga ttt ttg agg tgc aag aat atc att cat gta      389
Ile Ile Thr Gly Gly Gly Phe Leu Arg Cys Lys Asn Ile Ile His Val
       105                 110                 115

att ggt gga aat gat gtc aag agt tca gtt tcc tct gtt ttg cag gag      437
Ile Gly Gly Asn Asp Val Lys Ser Ser Val Ser Ser Val Leu Gln Glu
    120                 125                 130

tgt gaa aaa aaa aat tac tca tcc att tgc ctc cca gcc att ggg aca      485
Cys Glu Lys Lys Asn Tyr Ser Ser Ile Cys Leu Pro Ala Ile Gly Thr
135                 140                 145                 150

gga aat gcc aaa caa cac cca gat aag gtt gct gaa gcc ata att gat      533
Gly Asn Ala Lys Gln His Pro Asp Lys Val Ala Glu Ala Ile Ile Asp
               155                 160                 165

gcc att gaa gac ttt gtc cag aaa gga tca gcc cag tct gtg aaa aaa      581
Ala Ile Glu Asp Phe Val Gln Lys Gly Ser Ala Gln Ser Val Lys Lys
          170                 175                 180

gtt aaa gtt gtt atc ttt ctg cct caa gta ctg gat gtg ttt tat gct      629
Val Lys Val Val Ile Phe Leu Pro Gln Val Leu Asp Val Phe Tyr Ala
       185                 190                 195

aac atg aag aaa aga gaa ggg act cag ctt tct tcc caa cag tct gtg      677
Asn Met Lys Lys Arg Glu Gly Thr Gln Leu Ser Ser Gln Gln Ser Val
    200                 205                 210

atg tct aaa ctt gca tca ttt ttg ggc ttt tca aag caa tct ccc caa      725
Met Ser Lys Leu Ala Ser Phe Leu Gly Phe Ser Lys Gln Ser Pro Gln
215                 220                 225                 230
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Lys Lys Asn His Leu Val Leu Glu Lys Lys Thr Glu Ser Ala Thr Phe
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cgg gtg tgt ggt gaa aat gtc acg tgt gtg gaa tat gct atc tcc tgg      821
Arg Val Cys Gly Glu Asn Val Thr Cys Val Glu Tyr Ala Ile Ser Trp
            250                 255                 260

cta caa gac ctg att gaa aaa gaa cag tgt cct tac acc agt gaa gat      869
Leu Gln Asp Leu Ile Glu Lys Glu Gln Cys Pro Tyr Thr Ser Glu Asp
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gag tgc atc aaa gac ttt gat gaa aag gag tat cag gag ttg aat gag      917
Glu Cys Ile Lys Asp Phe Asp Glu Lys Glu Tyr Gln Glu Leu Asn Glu
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ctg cag aag aag tta aat att aac att tcc ctg gac cat aag aga cct      965
Leu Gln Lys Lys Leu Asn Ile Asn Ile Ser Leu Asp His Lys Arg Pro
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ttg att aag gtt ttg gga att agc aga gat gtg atg cag gct aga gat     1013
Leu Ile Lys Val Leu Gly Ile Ser Arg Asp Val Met Gln Ala Arg Asp
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gaa att gag gcg atg atc aag aga gtt cga ttg gcc aaa gaa cag gaa     1061
Glu Ile Glu Ala Met Ile Lys Arg Val Arg Leu Ala Lys Glu Gln Glu
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tcc cgg gca gat tgt atc agt gag ttt ata gaa tgg cag tat aat gac     1109
Ser Arg Ala Asp Cys Ile Ser Glu Phe Ile Glu Trp Gln Tyr Asn Asp
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aat aac act tct cat tgt ttt aac aaa atg acc aat ctg aaa tta gag     1157
Asn Asn Thr Ser His Cys Phe Asn Lys Met Thr Asn Leu Lys Leu Glu
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gat gca agg aga gaa aag aaa aaa aca gtt gat gtc aaa att aat cat     1205
Asp Ala Arg Arg Glu Lys Lys Lys Thr Val Asp Val Lys Ile Asn His
375                 380                 385                 390

cgg cac tac aca gtg aac ttg aac aca tac act gcc aca gac aca aag     1253
Arg His Tyr Thr Val Asn Leu Asn Thr Tyr Thr Ala Thr Asp Thr Lys
                395                 400                 405

ggc cac agt tta tct gtt cag cgc ctc acg aaa tcc aaa gtt gac atc     1301
Gly His Ser Leu Ser Val Gln Arg Leu Thr Lys Ser Lys Val Asp Ile
            410                 415                 420

cct gca cac tgg agt gat atg aag cag cag aat ttc tgt gtg gtg gag     1349
Pro Ala His Trp Ser Asp Met Lys Gln Gln Asn Phe Cys Val Val Glu
        425                 430                 435

ctg ctg cct agt gat cct gag tac aac acg gtg gca agc aag ttt aat     1397
Leu Leu Pro Ser Asp Pro Glu Tyr Asn Thr Val Ala Ser Lys Phe Asn
    440                 445                 450
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cag acc tgc tca cac ttc aga ata gag aag att gag agg atc cag aat     1445
Gln Thr Cys Ser His Phe Arg Ile Glu Lys Ile Glu Arg Ile Gln Asn
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cca gat ctc tgg aat agc tac cag gca aag aaa aaa act atg gat gcc     1493
Pro Asp Leu Trp Asn Ser Tyr Gln Ala Lys Lys Lys Thr Met Asp Ala
                475                 480                 485

aag aat ggc cag aca atg aat gag aag caa ctc ttc cat ggg aca gat     1541
Lys Asn Gly Gln Thr Met Asn Glu Lys Gln Leu Phe His Gly Thr Asp
            490                 495                 500

gcc ggc tcc gtg cca cac gtc aat cga aat ggc ttt aac cgc agc tat     1589
Ala Gly Ser Val Pro His Val Asn Arg Asn Gly Phe Asn Arg Ser Tyr
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gcc gga aag aat gcc gtg gca tat gga aag gga acc tat ttt gct gtc     1637
Ala Gly Lys Asn Ala Val Ala Tyr Gly Lys Gly Thr Tyr Phe Ala Val
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aat gcc aat tat tct gcc aat gat acg tac tcc aga cca gat gca aat     1685
Asn Ala Asn Tyr Ser Ala Asn Asp Thr Tyr Ser Arg Pro Asp Ala Asn
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ggg aga aag cat gtg tat tat gtg cga gta ctt act gga atc tat aca     1733
Gly Arg Lys His Val Tyr Tyr Val Arg Val Leu Thr Gly Ile Tyr Thr
                555                 560                 565

cat gga aat cat tca tta att gtg cct cct tca aag aac cct caa aat     1781
His Gly Asn His Ser Leu Ile Val Pro Pro Ser Lys Asn Pro Gln Asn
            570                 575                 580

cct act gac ctg tat gac act gtc aca gat aat gtg cac cat cca agt     1829
Pro Thr Asp Leu Tyr Asp Thr Val Thr Asp Asn Val His His Pro Ser
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tta ttt gtg gca ttt tat gac tac caa gca tac cca gag tac ctt att     1877
Leu Phe Val Ala Phe Tyr Asp Tyr Gln Ala Tyr Pro Glu Tyr Leu Ile
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acg ttt aga aaa taa cactttggta tccttcccac aaaattattc tccatttgta     1932
Thr Phe Arg Lys
615

catatctagt tgtaaaacaa gttttagctt ttttttttaa ttcctcttaa cagatttttc   1992

taatatccaa ggatcattct ttgtcgctga agtcagtctt tcttcagctt ctctttcata   2052

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Ala Ser Gly Asp Ile Thr Lys Glu Glu Ala Asp Val Ile Val Asn Ser
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Thr Ser Asn Ser Phe Asn Leu Lys Ala Gly Val Ser Lys Ala Ile Leu
65 70 75 80

Glu Cys Ala Gly Gln Asn Val Glu Arg Glu Cys Ser Gln Gln Ala Gln
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Gln Arg Lys Asn Asp Tyr Ile Ile Thr Gly Gly Gly Phe Leu Arg Cys
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Lys Asn Ile Ile His Val Ile Gly Gly Asn Asp Val Lys Ser Ser Val
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Ser Ser Val Leu Gln Glu Cys Glu Lys Lys Asn Tyr Ser Ser Ile Cys
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Leu Pro Ala Ile Gly Thr Gly Asn Ala Lys Gln His Pro Asp Lys Val
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Ala Glu Ala Ile Ile Asp Ala Ile Glu Asp Phe Val Gln Lys Gly Ser
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Ala Gln Ser Val Lys Lys Val Lys Val Val Ile Phe Leu Pro Gln Val
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Leu Asp Val Phe Tyr Ala Asn Met Lys Lys Arg Glu Gly Thr Gln Leu
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Ser Ser Gln Gln Ser Val Met Ser Lys Leu Ala Ser Phe Leu Gly Phe
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Ser Lys Gln Ser Pro Gln Lys Lys Asn His Leu Val Leu Glu Lys Lys
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Pro Tyr Thr Ser Glu Asp Glu Cys Ile Lys Asp Phe Asp Glu Lys Glu
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Leu Asp His Lys Arg Pro Leu Ile Lys Val Leu Gly Ile Ser Arg Asp
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545                 550                 555                 560

Leu Thr Gly Ile Tyr Thr His Gly Asn His Ser Leu Ile Val Pro Pro
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Ser Lys Asn Pro Gln Asn Pro Thr Asp Leu Tyr Asp Thr Val Thr Asp
            580                 585                 590

Asn Val His His Pro Ser Leu Phe Val Ala Phe Tyr Asp Tyr Gln Ala
        595                 600                 605

Tyr Pro Glu Tyr Leu Ile Thr Phe Arg Lys
    610                 615
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CLAIMS

1. An isolated polypeptide comprising a sequence selected from:

(iii) the amino acid sequence of SEQ ID NO: 2;

(iv) an allelic or species variant of a sequence of (i);

(iii) a variant of a sequence of (i) having at least 60% identity over the full length of SEQ ID NO: 2 and having substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity; or

(iv) a fragment of (i) or (ii) which does not have the amino acid sequence of SEQ ID NO: 4, an allelic or species variant of the sequence of SEQ ID NO: 4 or a fragment thereof and which retains substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity.

2. A variant or fragment of the polypeptide defined by the amino acid sequence set forth in SEQ. ID. No. 2 suitable for raising specific antibodies for said polypeptide and/or an allelic or species variant thereof.

3. A polynucleotide encoding a polypeptide as claimed in claim 1 or 2.

4. A polynucleotide as claimed in claim 3 which is a cDNA.

5. A polynucleotide encoding a polypeptide as claimed in claim 1, which polynucleotide comprises:

(a) the nucleic acid sequence of SEQ ID NO: 1 or the coding sequence thereof and/or a sequence complementary thereto;

(b) a sequence which hybridises to a sequence as defined in (a);

(c) a sequence that is degenerate as a result of the genetic code to a sequence as defined in (a) or (b); or

(d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c).

6. An expression vector comprising a polynucleotide sequence as claimed in any one of claims 3 to 5, which is capable of expressing a polypeptide according to claim 1 or 2.

7. A host cell containing an expression vector according to claim 6.

8. An antibody specific for a polypeptide as claimed in claim 1 or claim 2.

9. An isolated polynucleotide which directs expression *in vivo* of a polypeptide as claimed in claim 1.

10. A polypeptide as claimed in claim 1 or a polynucleotide as claimed in claim 9 for use in therapeutic treatment of a human or non-human animal.

11. A pharmaceutical composition comprising a polypeptide as claimed in claim 1 or a polynucleotide as claimed in claim 9 and a pharmaceutically acceptable carrier or diluent.

12. Use of a polypeptide as claimed in claim 1 or a polynucleotide as claimed in claim 9 in the preparation of medicament for use in therapy as an anti-viral, anti-tumour or immunomodulatory agent.

13. A method of treating a patient having a Type 1 interferon treatable disease, which comprises administering to said patient an effective amount of a polypeptide as claimed in claim 1 or a polynucleotide as claimed in claim 9.

14. A method of producing a polypeptide according to claim 1 or 2, which method comprises culturing host cells as claimed in claim 7 under conditions suitable for obtaining expression of the polypeptide and isolating the said polypeptide.

15. A method of identifying a compound having immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity comprising providing a cell capable of expressing the polypeptide of SEQ. ID. No. 2 or a naturally-occurring variant thereof having at least 60 % identity over the full length of SEQ ID NO: 2, incubating said cell with a compound under test and monitoring for upregulation of the gene encoding said polypeptide or variant.

16. A polynucleotide capable of expressing *in vivo* an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ. ID. No.2 or a naturally-occurring variant of said coding sequence having at least 60 % identity over the full length of said coding sequence for use in therapeutic treatment of a human or non-human animal.

17. An antibody as claimed in claim 8 for use in therapeutic treatment.

18. A set of primers for nucleic acid amplification which target sequences within a cDNA as claimed in claim 4.

19. A nucleic acid probe derived from a polynucleotide as claimed in any one of claims 3 to 5.

20. A probe as claimed in claim 19 which is attached to a solid support.

21. A method of predicting responsiveness of a patient to treatment with a Type 1 interferon, which comprises determining the level of the protein defined by the amino acid sequence set forth in SEQ. ID. No. 2 or a naturally-occurring variant thereof having at least 60 % identity over the full length of SEQ ID NO: 2, or the corresponding mRNA, in a cell sample from said patient, wherein said sample is obtained from said patient following administration of a Type 1 interferon or is treated prior to said determining with a Type 1 interferon in vitro.

22. A method as claimed in claim 21 wherein the interferon administered prior to obtaining said sample or used to treat said sample *in vitro* is the interferon proposed for treatment of said patient.

23. A method as claimed in claim 21 or claim 22 wherein a sample comprising peripheral blood mononuclear cells isolated from a blood sample of the patient is treated with a Type 1 interferon *in vitro*.

24. A method as claimed in any one of claims 21 to 23 wherein said determining comprises determining the level of mRNA encoding the protein defined by the sequence set forth in SEQ. ID. No. 2 or a naturally-occurring variant of said protein having at least 60% identity over the full length of SEQ ID NO: 2.

25. A non-human transgenic animal capable of expressing a polypeptide that is claimed in claim 1.

ABSTRACT

INTERFERON-α INDUCED GENE

The present invention relates to identification of a gene upregulated by interferon-α administration corresponding to the cDNA sequence set forth in SEQ. ID. No. 1. Determination of expression products of this gene is proposed as having utility in predicting responsiveness to treatment with interferon-α and other interferons which act at the Type 1 interferon receptor. Therapeutic use of the protein encoded by the same gene is also envisaged.